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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,546	03/26/2001	Deborah J. Good	P 0279282	9489

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 08/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,546	GOOD ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment and change of address filed 5-21-03 have been entered. Claims 7, 10-21 and 28-49 have been canceled. Claims 1, 2, 4 and 8 have been amended. Claims 1-6, 8, 9 and 22-27 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-6, 8, 9 and 22-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-6, 8, 9 and 22-27 are directed to a transgenic ungulate having a homozygous deletion or disruption of the prion gene via homologous recombination of heterologous DNA, such as neo marker gene, into the prion gene locus, a transgenic bovine or ungulate that bears a heterologous gene extraneous to the prion gene locus and under the control of a promoter for the production of a recombinant protein, the cloned transgenic ungulate, and the line of transgenic ungulate. Claims 8, 9 and 23-25 specify the transgenic ungulate bears a heterologous gene extraneous to the prion gene locus and said heterologous gene is under the control of mammay-specific promoter for production of a protein in the milk of said transgenic ungulate.

The specification discloses isolation of bovine prp gene and optimization of G418 drug selection of BEF cells transfected with pPNT vector. The specification teaches protocols for transfecting BEF cells with prp targeting vector and making of transgenic ungulate via nuclear transfer.

The claims encompass production of any transgenic ungulate, such as bovine, having homologous deletion of prion (prp) gene and using said transgenic ungulate lacking prion gene. The specification indicates that the transgenic ungulates of the present application can be used as the source of cells and tissues for xenotransplantation in treating diseases, such as Parkinson's disease or Huntington disease, or can be used for the production of a recombinant protein in milk. However, the specification fails to provide adequate guidance and evidence for what would be the resulting phenotype of the transgenic ungulate having homologous deletion of prion gene and how to use said transgenic ungulates. The specification fails to provide adequate guidance and evidence for the production and use of a transgenic ungulate or a line of transgenic ungulates having homologous deletion of prion gene.

The state of the art in the fields of transgenic animal at the time of the invention was unpredictable, the transgene expression and resulting phenotype of such expression is not always accurately predictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Similarly, it was unpredictable for generating transgenic animals harboring any disrupted gene. Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) pointed out that the approach of using ES

cells carrying a single-copy mutation of a specific gene to generate knockout transgenic animal is time-consuming and costly to obtain homozygous or double-knockout mice, and another major concern is the potentially lethal effect of the targeted gene. In some cases, gene knockout results in early death of embryos and young animals, or morphologically and functionally abnormal offsprings such as blind and/or handicapped animals.

Further, Sigmund, June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

In addition, Nishi et al., 1997 (The EMBO Journal, Vol. 16, No. 8, pp. 1858-1864) reports that nociceptin system plays a role in modulation of the nociceptive threshold and locomotor activity and shows that a transgenic mice lacking the nociceptin receptor does not result in significant differences in nociceptive threshold and locomotor activity as compared to control mice (e.g. abstract, introduction). In view of the reasons set forth above, the resulting phenotypes of the claimed transgenic ungulates having homologous deletion of prion gene would

be unpredictable at the time of the invention. Thus, one skilled in the art at the time of the invention would not know the resulting phenotypes of a transgenic ungulate having homologous deletion of prion gene and would not how to use said transgenic ungulates.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-6, 8, 9 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissmann et al., 1997 (Us Patent No. 5,698,763) in view of Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) and Shani et al., 1992 (Transgenic Research, Vol. 1, No. 5, p. 195-208).

Claims 1-6, 8, 9 and 22-27 are directed to a transgenic ungulate having a homozygous deletion or disruption of the prion gene via homologous recombination of heterologous DNA, such as neo marker gene, into the prion gene locus, a transgenic bovine or ungulate that bears a heterologous gene extraneous to the prion gene locus and under the control of a promoter for the production of a recombinant protein, the cloned transgenic ungulate, and the line of transgenic ungulate. Claims 8, 9 and 23-25 specify the transgenic ungulate bears a heterologous gene extraneous to the prion gene locus and said heterologous gene is under the control of mammay-specific promoter for production of a protein in the milk of said transgenic ungulate.

Weissmann teaches using DNA targeting molecules that specifically disrupt prp genes by homologous recombination in transfected animal cells, culturing the transfected animal cells, and producing transgenic mammals, such as sheep, pigs, and cattle, having deleted prp gene and the transgenic progeny of said mammals. Weissmann also teaches using neomycin or hygromycin selectable marker gene under the control of HSV TK promoter in the DNA targeting vector for selection of the transfected cells (e.g. abstract, column 6). Weissmann reports that complete prion genes have been cloned and sequenced and many have been found in mammals, such as human, mouse, cattle, sheep, goat and chicken, and teaches making transgenic mammals lacking PrP genes and thus devoid of prion proteins (e.g. column 1, 2). Weissmann produced a

transgenic mouse having homozygous deletion of the prp gene and showed its resistance to Scrapie infection (e.g. column 13, 14).

Weissmann does not teach using a heterologous gene, under the control of a mammary-specific promoter, extraneous to the prion gene locus and the production of a recombinant protein in the milk of the transgenic ungulate.

Wu teaches a method of making a transgenic knockout animal by using DNA targeting vector comprising hygromycin (hyg) or neomycin (neo), LaZ and HSV-TK selection marker genes, wherein hyg or neo, and LaZ genes are inserted into target gene locus via homologous recombination, however, the HSV-TK gene is outside the target gene locus (e.g. Figure 17.5-17.7).

Shani teaches generating transgenic mice expressing sheep beta-lactoglobulin (BLG) or human serum albumin (HSA) under the control of the sheep BLG promoter sequence and demonstrates that high levels of HSA can be expressed in the milk of transgenic mice. Shani uses the transgenic mice as a model system to test whether it is feasible of producing large quantity of HSA in the milk of transgenic livestock (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to include a heterologous gene as taught by Shani in the DNA targeting vector as taught by Weissmann and Wu for the production of a recombinant protein in milk because Wu teaches using hygromycin (hyg), neomycin (neo) or HSV-TK selection marker genes and Shani teaches using transgenic livestock to produce recombinant protein in milk and it was known in the art to express a heterologous gene in a transgenic animal for the production of its gene product and it would be obvious to one of ordinary skill.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to express a recombinant protein in the milk of a transgenic animal by using a mammary-specific promoter, such as beta-BLG promoter, as taught by Shani with reasonable expectation of success.

Applicants argue that the claims have been amended to read on ungulate having homozygous deletion of the prion gene and the Weissmann reference does not teach any ungulate prion gene sequencem therefore, it is not enabled to make the claimed transgenic ungulate without the prion gene sequence. Applicants further argue that Wu does not teach DNA construct for producing transgenic ungulate having homozybous deletion of the prion gene and Shani does not teach DNA sequence that can be used to generate the claimed transgenic ungulates (amendment, p. 6-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C 103(a) rejection. Weissmann does teaches that complete prion genes have been cloned and sequenced and many have been found in mammals, such as human, mouse, cattle, sheep, goat and chicken, and also teaches making transgenic mammals lacking PrP genes and thus devoid of prion proteins. Therefore, the prion gene sequence of cattle was known in the art and one ordinary skill in the art would know how to make the claimed transgenic ungulate according to the teachings Weissmann, Wu and Shani. Further, the claims do not specify the phenotypes of the transgenic ungulates, thus, one of ordinary skill would be able to make the claimed transgenic ungulate regardless the resulting phenotypes of said transgenic ungulates with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.